

LETTERS AND
CORRESPONDENCE

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Pernicious Anemia (PA) Subsequent to Insulin-Dependent Diabetes Mellitus and Idiopathic Thrombocytopenic Purpura, and Effects of Oral Cobalamin on PA

To the Editor: We describe here an aged female with a unique combination of [insulin-dependent diabetes (IDDM), pernicious anemia (PA), and idiopathic thrombocytopenic purpura (ITP)], who had antibodies to the thyroid gland, of suspected autoimmune etiology.

A 75-year-old woman presented with IDDM. One week after admission when hematological examinations showed no abnormal findings, her platelet counts had fallen to $35 \times 10^9/L$ as shown in Fig. 1. A diagnosis of ITP was made, although platelet counts increased to normal without treatment 1 week after the onset of thrombocytopenia. They remained within the normal range until her anemia was more pronounced when hematological data revealed macrocytic anemia with a red blood cell count of $2.33 \times 10^{12}/L$, hemoglobin concentration of 10.3 g/dl, hematocrit of 30.1%, reticulocyte count of $42.4 \times 10^9/L$, leukopenia with leukocyte count of $3.2 \times 10^9/L$, and thrombocytopenia with platelet count of $129 \times 10^9/L$. Peripheral blood film showed hypersegmentation of neutrophils, and bone marrow examination revealed megaloblastic erythropoiesis and giant metamyelocytes. The serum cobalamin level was low (140 pg/ml, normal 249–938 pg/ml). Both anti-intrinsic factor (IF) and anti-parietal cell antibodies were present. Findings on other immune work-up were all negative except for anti-thyroglobulin, anti-thyroid peroxidase, anti-insulin, anti-glutamic acid decarboxylase antibodies, and microsome test. A diagnosis of PA was made and the patient was treated with oral hydroxycobalamin. The peaks of reticulocyte counts occurred 6 days after the initiation of the treatment. Platelet counts and the levels of serum lactate dehydrogenase reached normal levels within 7, and 12 days after the treatment, respectively. The

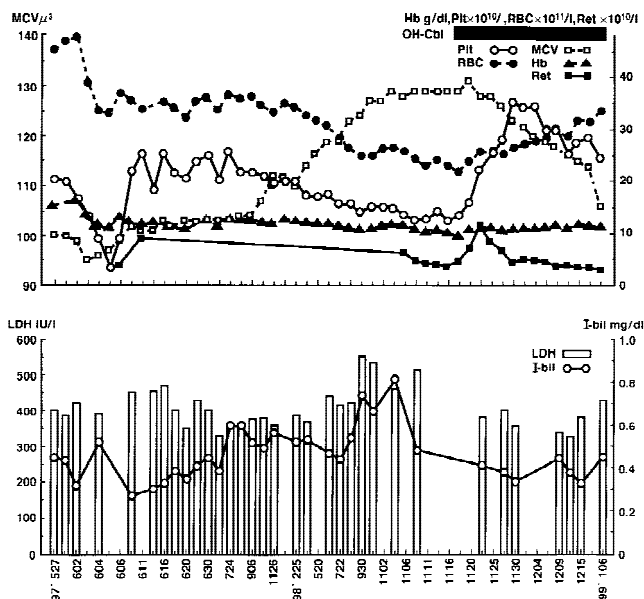


Fig. 1. The temporal relationships between the hydroxycobalamin given, the hematological, LDH and I-bil levels, and the clinical course of the patient. OH-Cbl, hydroxycobalamin; I-bil, indirect bilirubin; LDH, lactate dehydrogenase; MCV, mean corpuscular volume.

mean corpuscular volume decreased to the normal range 2 months after the treatment.

The association between DM and PA has been well known. The incidence of frank PA among diabetics, most of whom are insulin-dependent, is 3.9/1,000 [1] compared with 1.27/1,000 in the general population. Several reports have suggested an association between diabetes, or PA and thyroid disorders. Our patient had thyrogastric antibodies as shown by a report in which the antibodies are frequently found in patient with IDDM [2]. The finding that she also had anti-IF antibody is in accordance with the observation which suggested an increase prevalence of anti-IF antibody in the diabetic population [3]. Autoimmune cytopenia in PA has been described previously. All of the patients with coexisting ITP reported by Rabinowitz et al. [4] were women with blood type O. The incidental association of sex and blood type O in the patient reported here is intriguing. This case suggests that laboratory screening of individuals with auto-antibodies should be extended to anticipate a wider range of hematological autoimmune conditions, and emphasizes the clinical and immunogenetic links between the autoimmune diseases.

Intramuscular injection of cobalamin is conventionally used for the treatment of cobalamin deficiency, although we recently reported the beneficial effects of oral cobalamin for the disorder [5]. Large daily oral doses of hydroxycobalamin were effective in producing hematological responses in this case. The patient reported here would be less compliant with parenteral use of cobalamin because she would have to take insulin for the rest of her life. This fact substantiates the beneficial effect of oral cobalamin treatment for PA.

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A 78-Year-Old Man With Sickle-Cell Anemia

To the Editor: Sickle-cell anemia is caused by a single amino acid substitution but the clinical picture is marked by considerable variations in severity, largely because of unknown genetic and environmental influences. Here we describe a patient with sickle-cell anemia who died at the age of 78 from urosepsis.

A 78-year-old African-American man was admitted in December 1996 because of swelling of the legs and weak urinary stream. He had been diagnosed as having sickle-cell anemia at age 36, but had never had a pain crisis and was transfused only once. In 1980, his Hb was 9.0 g/dl, and reticulocytes 16%. The blood smear showed numerous sickled erythrocytes. Hemoglobin electrophoresis showed Hb S (97%) and absence of Hb A. Fetal hemoglobin measured <1%. In May 1996, he was found to have chronic cor-pulmonale and congestive heart failure. He was treated with transfusion of packed erythrocytes, diuretics, and erythropoietin injections.

At his admission in December 1996, he was afebrile with a pulse of 100. Other findings were icterus, jugular venous distention, bilateral leg edema, a right leg ulcer, and hepatomegaly. He had mild proteinuria and pyuria, anemia (Hb 5.8 g/dl), and renal insufficiency (creatinine 3.0 mg/dl). Ultrasonography of the kidneys showed bilateral pyelocaliectasis. The post-voiding residual urine volume was 1000 ml. Three days following insertion of an in-dwelling Foley's catheter, the patient developed *Escherichia coli* sepsis complicated by multiorgan failure and died on the 40th hospital day. Autopsy showed biventricular hypertrophy, medial hypertrophy of the pulmonary arterioles with plexiform changes, fibrinous pericarditis, macronodular cirrhosis, cholelithiasis, absence of spleen, and benign prostatic hypertrophy.

Results obtained from both Bsu36I digestion, and direct DNA sequencing of exon 1 of the patient's β -globin genes showed a typical sickle mutation (β 6Glu to β 6Val). A Southern blot analysis of the α gene cluster by using *EcoRI*, *BglII*, and *BamHI* showed a single α -globin gene deletion (-3.7 kb, "rightward") on one chromosome. Characterization of the haplotype of the patient's DNA sequences upstream of the β -globin DNA [1] showed homozygosity for the Benin haplotype. The normal body habitus and the lack of pain crises and congestive heart failure are features noted previously among long survivors with sickle-cell anemia [2,3]. Our patient is the oldest reported with sickle-cell anemia. The co-inheritance of α -thalassaemia does not appear to have a demonstrable effect on the mortality from sickle-cell anemia [4]. High levels of fetal haemoglobin, and the

inheritance of Arab-Indian or Senegal haplotype are predictors for improved survival in sickle-cell disease [5]. Interestingly, these favorable prognostic factors were absent in our patient and in the few patients reported with sickle-cell anemia surviving into their eighth decade [3]. The long-surviving patients with sickle-cell anemia with a benign clinical course are a reminder to the physician/researcher that there is much that is unknown about this (arguably) the most investigated molecular disease.

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Splenic Infarction From Factor V Leiden Mutation

To the Editor: Over the past decade, thrombophilia from anticardiolipin antibody, protein C deficiency, lupus anticoagulant and prothrombin 20210A polymorphism have emerged as additional causes of splenic infarction. There are several published case reports of splenic infarction in the setting of thrombophilia. We describe a patient with splenic infarction associated with a factor V Leiden gene mutation.

A 34-year-old white woman was referred to our outpatient Hematology office for evaluation of thrombophilia. Six weeks prior to her office visit, she awakened from sleep because of left upper quadrant abdominal pain. She also experienced vomiting and diarrhea. She was admitted to the hospital because of worsening symptoms. A computed tomography scan of the abdomen revealed splenic infarction. She was treated with intravenous fluids and meperidine. A week later, she was discharged from the hospital with minimal abdominal pain controlled with oral hydrocodone. She was checked for a possible thrombophilia and testing revealed abnormal APC resistance ratio.

The patient's past history was notable for 35 years pack of smoking a pack per day and a 4 year use of oral contraceptives. She had two preg-

nancies with one spontaneous abortion. Her mother developed arterial thrombotic events: A cerebrovascular accident in her 50s and death from a myocardial infarction in her 60s. The patient's sister had suffered a spontaneous first trimester miscarriage and was found to be heterozygous for the factor V Leiden gene mutation.

In the office visit she had tenderness in the left upper quadrant of the abdomen. A repeat CT scan 6 weeks after her first showed partial resolution of the low density area in the location of the presumed splenic infarction. Prothrombin time, aPTT, lupus anticoagulant screen; plasma levels of antithrombin III, factor II, protein C, protein S total and free, anticardiolipin antibodies, and homocysteine were within normal limits. The activated protein C resistance ratio was 1.1 (normal ratio > 2.3) and further analysis showed that she was heterozygous for factor V Leiden by polymerase chain reaction.

Because the patient had two coexisting risk factors—cigarette smoking and oral contraceptives—that increased the risk for thromboembolism in the setting of a factor V Leiden mutation, we decided to promote risk factor reduction rather than long term anticoagulation after this initial event. The patient did stop smoking and is no longer taking oral contraceptives. There has been no further thromboembolic event 6 months after the initial splenic infarct.

Factor V Leiden heterozygotes have a 7-fold risk of DVT [1]. Identifiable risk factors and factor V Leiden mutation increase the risk of thromboembolic events. Oral contraceptives increase the risk by 35-fold [2] and tobacco increases the risk of developing myocardial infarction by 32-fold [3]. Clearly, our patient was in a precarious situation for developing thrombosis. In her case, she had a splenic infarction.

Patients with inheritable thrombophilia should eliminate all reversible risk factors. Then the issue of anticoagulation should be addressed. Those experiencing a first episode of VTE are maintained on warfarin for 6 months [4] with an International Normalization Ratio between 2.0 to 3.0. Indefinite anticoagulation is recommended for patients with two or more spontaneous thromboses, one spontaneous life-threatening thrombosis or at an unusual site or in the presence of more than a single biologic defect [5]. Prolonged use of warfarin after six months should be weighed against the risk of hemorrhage.

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Possible Cyclosporin–Danazol Interaction in a Patient With Aplastic Anaemia

To the Editor: Cyclosporin (Csa) is an immunosuppressive drug used in the treatment of aplastic anaemia. This drug has some serious side-effects: nephrotoxicity, hypertension, hepatotoxicity and neurotoxicity. These effects depend on the dose administered and are related to concentrations in blood greater than 400 ng/ml [1]. Csa is a drug which is eliminated mainly by hepatic metabolism. When it is administered in combination with inductive or inhibitor drugs, there may be pharmacological interaction with clinical repercussion. In this paper, we describe a case of interaction of Csa and an anabolic steroid Danazol (Dnz), used together to treat an adult patient with aplastic anaemia, which resulted in an increase in the Csa blood level.

A 28-year-old man diagnosed aplastic anaemia, undergoing treatment with Csa at a dose of 250 mg/day administered orally and with Csa blood level, between 150–250 ng/ml. He was then also given Dnz (200 mg/8 hr). Coinciding with the addition of Dnz, a 38% increase in the level of Csa was produced which obliged us to reduce the dose of Csa to 200 mg/day. With this Csa dose and maintaining the Dnz dose constant, the Csa blood level returned to normal and was maintained in subsequent controls. Therefore, it was possible to continue the Csa-Dnz combination (Table 1). Throughout the treatment, there were no signs of nephrotoxicity, hepatotoxicity, hypertension or neurological alterations. Csa blood levels were measured by a monoclonal TDX assay.

In this paper, we describe the Csa-Dnz interaction which led to an increase in the Csa blood levels, and a 50% decrease in the Csa dose/Blood level ratio. Dnz is an inhibitor of the P-450 cytochrome responsible for the metabolism of Csa. Administering Dnz in association with Csa led to a decrease in the hepatic clearance of Csa with a consequent increase in blood levels [2].

By using Medline, we reviewed the literature (1968–1998) and found 4 cases of Csa-Dnz interaction. In some of the cases published, the combined use of both drugs gave rise to Csa levels of over 400 ng/dl, associated with an increase in serum creatinine [3] or in serum creatinine and hepatic enzymes [4] and the appearance of moderate diastolic hypertension [5] which made it necessary to suspend treatment with Dnz and Csa in combination.

In our case, therapeutic drug monitoring of Csa blood levels permitted

TABLE I. Doses and Cyclosporin Plasma Levels Before and After Combination With Danazol

Day	Dose (mg/d)	Cyclosporin blood levels (ng/ml)	Dose/blood level ratio	Serum creatinine (mg/d)
1	250	188	1.32	1
15	250	228	1.09	0.9
21	250	219	1.14	1
43	250	223	1.12	1
<i>Commencement of treatment with 200 mg of Danazol every 8 hr</i>				
64	250	360	0.55	1.2
77	200	214	0.93	1.3
90	200	234	0.85	1.3

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early detection of Csa-Dnz interaction and the Csa levels rose to 360 ng/ml without involving nephro- or hepatotoxicity. By adjusting the dose we were able to continue administering both drugs. In view of this case and the increasing use made of Csa and Dnz in combination to treat aplastic anaemia, it is advisable to systematically reduce the Csa dose when treatment with Dnz is commenced and to therapeutic drug monitoring the Csa levels so as to quantify the inhibiting effect of Dnz on the metabolism of Csa. The Csa dose should then be adjusted to obtain blood levels within the therapeutic range, thus enabling both drugs to be used safely in the treatment of aplastic anaemia.

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